DEPARTMENT OF HEALTH & HUMAN SERVICES

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CBER-03-004

Food and Drug Administration
Rockville MD 20857

WARNING LETTER

December 19, 2002

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Mr. John P. Wareham
President and Chief Executive Officer
Coulter Corporation
4300 North Harbor Boulevard
P.O. Box 3100
Fullerton, CA 92834

Dear Mr. Wareham:

The Food and Drug Administration (FDA) conducted an inspection of Coulter Corporation (Coulter), located at 560 West 20th Street and 740 West 83rd Street, Hialeah, Florida, from June 4 to June 28, 2002. During the inspection, our investigators documented violations of Section 501(h) of the Federal Food, Drug, and Cosmetics Act and Title 21, Code of Federal Regulations (CFR), Subchapter F, Parts 600-680 and Subchapter H, Part 820. These documented violations include, but are not limited to, the following:

1. Failure to promptly report biological product deviations (BPD) that may have affected the safety, purity, or potency of any distributed product [21 CFR 600.14(a)]. You did not submit BPD reports for the following:

   a. You received numerous customer complaints concerning elevated optical density (OD) readings for the negative control used in the Coulter HIV-1 p24 Antigen Assay and/or the [redacted] HIV-1 p24 Antigen ELISA Test System (HIV-1 p24 assays). Customers reported that OD readings for the negative control in numerous distributed lots exceeded the package insert specification of OD less than or equal to [redacted]. BPD reports concerning these deviations have not been submitted to the Center for Biologics Evaluation and Research (CBER).

   b. During [redacted] testing performed on stability samples of HIV test kit components from January 24 to March 15, 2001, the [redacted] agents in the Normal Human Serum (NHS) lot 2059L864 were not found to be effective against all bacterial strains from the USP

[redacted]

c. You did not notify CBER of a change to the method of loading standard dilutions into microwells for the testing of the Normal Human Serum Pool. The change to the method of loading standard dilutions was made as a result of a failure investigation. Operators are now instructed to load standard dilutions of the backlot and testlot alternately into the microwells for testing of the Normal Human Serum Pool.

d. You did not notify CBER of changes to lot release panels. For example, the replacement of lot release panel member K5 with K7; or the replacement of lot release panel member J4 with J8.

3. Failure to establish and maintain adequate procedures for implementing corrective and preventive action, including requirements for identifying the action(s) needed to correct and prevent recurrence of nonconforming product and other quality problems [21 CFR 820.100(a)(3)], in that:

a. You have received numerous customer complaints concerning an increased incidence of initial reactive results for your HIV-1 p24 assays. The rates of initial reactive results for numerous lots did not conform to the initial reactive rates stated in the labeling claims for these assays. Although an investigation has been ongoing since August 1998 to investigate the cause of the increased incidence of initial reactive results, effective corrective action has not been implemented and you continue to receive complaints concerning an increased incidence of initial reactive results for your HIV-1 p24 assays.

b. You have received numerous customer complaints concerning elevated OD readings for the negative control used in your HIV-1 p24 assays. Customers have reported that OD readings for the negative control in numerous distributed lots exceeded the package insert specification of OD less than or equal to 0.100. Although at least four investigations have been opened since June 2000 to investigate the cause of the elevated OD readings for the negative control, effective corrective action has not been implemented and you continue to receive complaints concerning elevated OD readings for the negative control used in your HIV-1 p24 assays.

4. Failure to establish, maintain, and follow procedures to prevent contamination of product by substances that could reasonably be expected to have an adverse effect on product quality [21 CFR 820.70 (e)], in that:

a. [redacted] testing was performed on stability samples of distributed HIV test kit components from January 24 to March 15, 2001. The antimicrobial agents in Normal Human Serum (NHS) lot 2059L864

were not found to be effective. The criteria for determining an effective formulation as stated in your SOP 283-042 Rev A entitled "Preservative Effectiveness Testing" were not met, in that the formulation was not found to be effective against all bacterial strains from the USP standard panel.

b. [redacted] testing was performed on stability samples of distributed HIV test kit components from February 6 to March 12, 2002. The antimicrobial agents in Negative Control lot 2050H024 were not found to be effective. The criteria for determining an effective formulation as stated in your SOP 283-042 Rev A were not met, in that the formulation was not found to be effective against all bacterial strains from the USP standard panel.

5. You reworked products, such as relabeling vials of kit reagents initially labeled with incorrect expiration dates, relabeling kit reaction plates initially bearing labels with partially handwritten lot numbers, and inserting Lot Number/Expiration Date Assay Sheets into kits missing the Assay Sheets, but you did not establish and maintain procedures for rework, to include retesting and reevaluation of the nonconforming product after rework in order to ensure that the product meets its current approved specifications [21 CFR 820.90 (b)(2)].

We acknowledge receipt of your written response, dated July 22, 2002, to the Form FDA-483 issued on June 28, 2002. We have reviewed your response and the accompanying attachments. Corrective actions addressed in your July 22, 2002 response may be referenced in your reply to this letter, as appropriate. We have the following specific comments concerning your response. The items correspond to the observations listed on the Form FDA-483.

FDA-483 item #2

Your response states that you believe your existing procedure PCA-010 entitled "Biological Product Deviation Reporting" adequately establishes a process for reporting deviations in accordance with 21 CFR 600.14. However, BPD reports are not being submitted to CBER as required by the regulation. Please comment.

FDA-483 items #3, #4, and #5

Your response states that you are committed to conducting thorough and timely investigations while taking into account the nature and potential impact of the event being investigated. However, there is no evidence that effective corrective action has been implemented for many of the issues addressed by FDA-483 items #3, #4, and #5. Furthermore, you are continuing to receive customer complaints concerning many of these same issues.

The Quality System Regulation (QS Reg) requires device manufacturers to investigate the causes of nonconformities relating to their products, and to identify the actions needed to correct and prevent recurrence of nonconforming product and other quality

problems. Manufacturers are further required to verify or validate the corrective and preventive action to ensure that such action is effective and does not adversely affect the finished product. When quality problems are reported to manufacturers as product complaints, the QS Reg requires manufacturers to review and evaluate complaints in a timely manner and to initiate an investigation, as necessary.

FDA-483 item #6

Your response states that you believe your existing procedure PMN-019 entitled "USA Pre-Market Notification – Changes to Biological Products" is adequate. However, CBER is not being notified of changes in the product, production process, quality controls, equipment, and labeling established in your approved license as required by the regulation. Please comment.

FDA-483 item #7

Your response states that you utilize the USP Standard Panel in your preservative effectiveness protocol, and your SOP 283-042 Rev A entitled "Preservative Effectiveness Testing" requires you to follow USP's preservative effectiveness interpretation, requiring that (a) preservatives reduce the concentrations of viable bacteria to not more that 0.1% of the initial concentrations by the fourteenth day; (b) the concentrations of viable yeasts and molds remain at or below the initial concentrations during the first 14 days; and (c) the concentration of each test microorganism remains at or below these designated levels during the remainder of the 28-day test period. However, despite your response, and the express requirement in your SOP, you do not follow these acceptance criteria, which we believe are appropriate to assure the safety, purity, and potency of your HIV-1p-24 assays.

FDA-483 item #10

Your response states that the validation and verification data/reports for the use of the [redacted] during the manufacturing process in the mixing of [redacted] and the [redacted] were submitted to CBER in the annual report covering the period March 14, 2001 through March 13, 2002. The response further states that your data demonstrates that your product would continue to meet performance specifications. Comments on the adequacy of the validation and verification data/reports for the use of the [redacted] will be provided under separate correspondence by CBER's Office of Blood Research and Review, as necessary.

Neither this letter nor the observations noted on the Form FDA-483 are intended to be an all-inclusive list of the deficiencies at your facilities. It is your responsibility to assure that your operations are in full compliance with all applicable Federal laws and regulations.

You should take prompt action to correct these deviations. Failure to promptly correct these deviations may result in regulatory action without further notice. Such action may include license suspension and/or revocation, seizure and/or injunction, and/or civil penalties.

Federal agencies are advised of the issuance of all Warning Letters about drugs and devices so that they may take this information into account when considering the award of contracts.

Please notify this office in writing within fifteen (15) working days of receipt of this letter of any steps you have taken or will take to correct the noted deviation and to prevent their recurrence. If corrective actions cannot be completed within 15 working days, state the reason for the delay and the time within which the corrections will be completed.

Your response should be sent to the Food and Drug Administration, Center for Biologics Evaluation and Research, 1401 Rockville Pike, Suite 200 N, Rockville, Maryland 20852-1448, Attention: Division of Case Management, HFM-610. If you have any questions regarding this letter, please contact Ms. Mary Malarkey, Director, Division of Case Management, at (301) 827-6201.

Sincerely,

Sandra N. Whetstone
Acting Director
Office of Enforcement

cc: